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Introduction

Cell Mechanisms and Cell Biology

> In order to succeed in solving these various problems, one must so to speak progressively dismantle the organism, as one takes to pieces a machine in order to recognize and study all its works.
>
> (Bernard, 1865, Part II, Chapter 1)

1. A DIFFERENT KIND OF SCIENCE

To many people, cell biology is an unlikely domain to impart impetus for a major shift in the way philosophy of science is practiced. Cells appear to be the object of straightforward empirical observation, not of bold theories that challenge the status quo. In high school or at the museum you look into the microscope and struggle to see what you are told you should see – structures that are never as sharp and well delineated as in the drawings in textbooks. What could cell biology be but a tedious descriptive science? This popular conception, however, is quite erroneous. Cells, as Theodor Schwann first concluded in the 1830s, are the basic units of life. They perform all essential vital functions: extracting energy and building materials from their environment, constructing and repairing themselves and synthesizing products for export, regulating their own internal operations, reproducing themselves periodically by dividing, cleaning up their own waste, and so forth. Beginning in the 1940s an initially small cadre of investigators who were pioneers in the modern discipline of cell biology began to figure out the biochemical mechanisms that enable cells to perform these functions. Although miniaturized, the mechanisms they found to be operative in each cell are staggeringly complex. Their work and that of their successors, primarily in 1940–70, revolutionized our understanding of the basic processes of life. Now, half a century later,

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I am drawing on that lively period of scientific enterprise to find fuel for yet another revolution, one that focuses on the very conception of science itself.

The science of cell biology is very different from the textbook image of science, including that advanced in traditional philosophy of science. That picture, grounded on some of the great successes of the scientific revolution and subsequent developments in some areas of physics, emphasizes bold unifying generalizations – the laws of nature. Newton's laws of motion promised to explain all motion, both terrestrial and celestial. The laws of thermodynamics and electromagnetism are similarly broad in their sweep. In biology, Darwin's insight that evolution by natural selection occurs when there is heritable variation in fitness (Lewontin, 1970) has provided a similarly powerful unifying generalization. However, most areas of biology – including cell biology – do not fit into this picture. Instead of unifying generalizations, cell biology offers detailed accounts of complex mechanisms in which different component parts perform specific operations, which are organized and orchestrated so that a given type of cell can accomplish the functions essential for its life. Not elegant generalizations, but exquisitely detailed accounts of mechanisms, are the products. This difference in product has broad implications for our overall understanding of science, including the challenges of generating evidence, advancing new hypotheses and theories, and evaluating and revising them.

In proposing an alternative characterization of science as the search for mechanisms, I am not seeking to eradicate the old picture of science as the quest for bold generalizations but to complement it. There are domains in which the Newtonian vision is appropriate – ones in which the aim of inquiry is best served by far-reaching generalizations that can be economically stated, often in a single equation. In many domains, though, the aim of inquiry leads to meticulous accounts of complex mechanisms. This is particularly true in the functional domains of biology – cell biology, molecular biology, physiology, pathology, developmental biology, neurobiology – and also in related areas of physics (biophysics) and chemistry (biochemistry). It does not advance our understanding of these sciences to impose an ill-fitting model. Rather, we need to develop a conception of science that is appropriate for them. Only then can we adequately address some of the traditional questions about science – what it is to explain a phenomenon, how explanations are discovered, and how they are evaluated.

The idea that much of science is a quest to articulate mechanisms is not news to biologists. Frances Crick (1988, p. 138) put it succinctly:

"What is found in biology is *mechanisms*, mechanisms built with chemical components . . ." Biologists do not always reach as far down as chemistry in characterizing biological mechanisms, but they do use the term *mechanism* naturally and often. A search I undertook of titles of articles in *Science* from 1880 to 1998 revealed 656 articles that included *mechanism*, *mechanisms*, or *mechanistic* in their titles. Only one appeared before 1900, and that concerned a psychological mechanism. Titles referring to biological mechanisms began in 1904 and are far more frequent than articles about non-biological mechanisms. They also outnumber articles that include *theory*, *theories*, or *theoretical* (584) or *law* or *laws* (165) in their title (the count for law discounted 25 titles clearly referring to political laws). A few of the early papers referring to mechanisms in their titles involved the vitalism–mechanism controversy that was still very active at the turn of the twentieth century. Most, however, focused on specific biological mechanisms. The following are some illustrative examples:

Edwin G. Conklin (1908). The mechanism of heredity.
Frank R. Lillie (1913). The mechanism of fertilization.
E. Newton Harvey (1916). The mechanism of light production in animals.
Jacques Loeb (1917). A quantitative method of ascertaining the mechanism of growth and of inhibition of growth of dormant buds.
W. J. V. Osterhout (1921). The mechanism of injury and recovery of the cell.
John H. Northrop (1921). The mechanism of an enzyme reaction as exemplified by pepsin digestion.
F. H. Pike and Helen C. Coombs (1922). The organization of the nervous mechanism of respiration.
Caswell Grave and Francis O. Schmitt (1924). A mechanism for the coordination and regulation of the movement of cilia of epithelia.

These titles reveal an interesting variation in generality, with Conklin discussing *the* mechanism of heredity while Grave and Schmitt discuss *a* mechanism within a particular cell type. The latter reflects the sort of engagement of individual scientists and research teams that became the norm in the twentieth century. Individual scientists and research teams honed in on much more delimited phenomena at a scale that can be fruitfully investigated in a single laboratory across a period of perhaps a few years. At the general level a broad research community might devote itself to a general phenomenon such as protein synthesis and seek to identify the general nature of the mechanism of protein synthesis. Specific researchers, though, focus on particular components of the mechanism or on the mechanism that is operative in particular cells or particular organisms. This is reflected by considering some typical

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titles of papers referring to mechanisms and protein synthesis in their titles[1] in the period 1950 to 1970:

Winnick, T. (1950). Studies on the mechanism of protein synthesis in embryonic and tumor tissues. I. Evidence relating to the incorporation of labeled amino acids into protein structure in homogenates. *Archives of Biochemistry*, 27, 65–74.

Novelli, G. D. and Demoss, J. A. (1957). The activation of amino acids and concepts of the mechanism of protein synthesis. *Journal of Cell Physiology,* 50 (Supplement 1), 173–97.

Yoshida, A. (1958). Studies on the mechanism of protein synthesis: bacterial alpha-amylase containing ethionine. *Biochimica et Biophysica Acta*, 29, 213–4.

Goodman, H. M. and Rich, A. (1963). Mechanism of polyribosome action during protein synthesis. *Nature,* 199, 318–22.

Griffin, B. E. and Reese, C. B. (1964). Some observations on the mechanism of the acylation process in protein synthesis. *Proceedings of the National Academy of Sciences, USA*, 51, 440–4.

Carey, N. H. (1964). The mechanism of protein synthesis in the developing chick embryo. The incorporation of free amino acids. *Biochemical Journal,* 91, 335–40.

Mano, Y. and Nagano, H. (1966). Release of maternal RNA from some particles as a mechanism of activation of protein synthesis fertilization in sea urchin eggs. *Biochemical and Biophysical Research Communications,* 25, 210–15.

Although the conception of a mechanism is widely invoked in the biological sciences, it has only recently become the target of philosophical inquiry. Chapter 2 will articulate the conceptions of mechanism and mechanistic explanation that figure in biology, especially cell biology. The quest to understand nature mechanistically has its roots in the scientific revolution and, although challenged by vitalist critics, figured prominently in the attempts to understand physiological systems throughout the eighteenth and nineteenth centuries. The key to the mechanistic approach was not the analogy of physiological systems to human made machines, but the quest to explain the functioning of whole systems in terms of the operations performed by their component parts. Beginning with Bernard, biologists also recognized the importance of the way in which the parts and their operations were organized. Increasingly, biology became a science in which phenomena were explained by discovering the organized parts and operations by which a mechanism performed its function.

[1] Another interesting class of papers uses the term mechanism not for the general phenomenon, protein synthesis, but for the way in which a particular substance alters that phenomenon. A characteristic example is the following: de Kloet, S., van Dam, G., and Koningsberger, V. V. (1962). Studies on protein synthesis by protoplasts of Saccharomyces carlsbergensis. III. Studies on the specificity and the mechanism of the action of ribonuclease on protein synthesis. *Biochimica et Biophysuca Acta*, 55, 683–9.

As I explore in Chapter 2, recognizing that the goal of many scientific inquiries is to describe the mechanism responsible for the phenomenon of interest provides a different perspective on many aspects of scientific inquiry. Diagrams often provide the most fruitful way of representing a mechanism, in which case scientists may relate the mechanism to the phenomenon of interest by mentally simulating its operation. In part this involves a reductionistic strategy of decomposing the mechanism into its parts and operations, but equally significant is figuring out how these are organized to work together and how various environmental conditions affect the mechanism's functioning. Finally, although traditional philosophy of science has had little to say about the process of discovery, when the focus is on mechanisms we can set out what the challenge of discovery is and analyze typical experimental strategies – strategies that figured prominently in discovering cell mechanisms.

2. THE ORGANIZATION OF SCIENCE INTO DISCIPLINES[2]

Although a central feature of my discussion will be the discovery of cell mechanisms, my broader focus is on the establishment of cell biology as a discipline. In 1940 no one would have listed cell biology when identifying scientific disciplines. By 1970 it was a well-established discipline. My goal is to trace and account for this change. First, though, a preliminary issue must be addressed. The word *discipline* is familiar enough, but what exactly is a scientific discipline? In the disciplines that analyze science (philosophy of science, history of science, and sociology of science, which are collectively referred to as *science studies*), a variety of criteria have been offered.

Perhaps the most common way in which people identify disciplines is in terms of the objects they investigate. Thus, astronomy is described as the study of suns, planets, and the like, whereas psychology investigates mental activities or behaviors. Dudley Shapere captured this feature of our ordinary conception of disciplines when he introduced the term *domain* for "the set of things studied in an investigation" (Shapere, 1984, p. 320; for his classic treatment of domains, see Shapere, 1974). Shapere's conception of a domain is more sophisticated than the lay conception, however, for he argued that domains are not simply presented to scientists but result from their decision as to what items (his term for the constituents of domains) to group together to constitute a domain. Thus, he showed how during the nineteenth century chemists made facts about basic elements a domain for study, because they

[2] The discussion in this section draws in part upon Bechtel (1986a).

construed them as the constituents of ordinary substances. Crucially, Shapere drew attention to the fact that scientists' reasons for grouping items together into a common domain may change over time. Moreover, as Toulmin noted, an item may be grouped with different items into different domains depending on the questions asked, and different investigators may ask different questions:

> If we mark sciences off from one another (using Shapere's term) by their respective 'domains', even these 'domains' have to be identified, not by the types of objects with which they deal, but rather by the questions which arise about them. Any particular type of object will fall in the domain of (say) 'biochemistry' only in so far as it is a topic for corresponding 'biochemical' questions; and the same type of object will fall within the domains of several different sciences, depending on what questions are raised about it. The behavior of a muscle fibre, for instance, can fall within the domains of biochemistry, electrophysiology, pathology, and thermodynamics, since questions can be asked about it from all four points of view . . . (1972, pp. 149)

While the objects of study are an important part of what characterizes a discipline, both Shapere and Toulmin made it clear they are insufficient. To identify the set of objects comprising the domain of a discipline, we need to consider why scientists group them together. Scholars who study science generally split over two approaches to addressing this issue, roughly differentiated by their respective disciplines. Philosophers and historians of ideas adopt what is often characterized as an *internalist* approach to understanding science, emphasizing cognitive factors such as theories and evidence, while sociologists and social historians adopt an *externalist* approach, focusing on social and institutional factors. In the 1970s and 1980s these two approaches were often portrayed as competing and mutually exclusive; more recently, many in science studies have recognized a role for both.

Through most of the twentieth century, philosophers of science focused on the theories advanced by scientists and the relation theories bore to evidence. To the extent that disciplines were considered at all, they were characterized in terms of theories. For example, in discussions of the unity of science – the question of how different sciences related to one another – the logical empiricists identified disciplines with their theories and asked whether they could be related to one another logically. Thus, the question of the relation of biology to physics and chemistry became the question of whether the theories (laws) of biology could, with the aid of bridge principles and boundary conditions, be derived from those of chemistry and physics (Oppenheim & Putnam, 1958; Nagel, 1961). If so, biology was said to be *reduced* to, and thereby unified with, physics.

Finding this singular focus on theory misguided, a number of philosophers have proposed alternative accounts that are more multifaceted and naturalistic. Best known is Kuhn's (1962/1970) notion of a *paradigm* and distinction between *normal science* and times of *paradigm shift*. In its more restricted sense, a paradigm for Kuhn was an exemplar – a solution to a particular problem that became a model for solving other problems. In its more extended sense, a paradigm was a general theory or theory schema that characterized a domain, identified problems to be solved, and specified strategies for solving them and criteria for evaluating proposed solutions. Kuhn's notion of a paradigm (both the restricted sense of an exemplar but especially the extended sense of a general theory) provided a way to characterize a group of scientists engaged in a similar enterprise and to tell a historical narrative of how the enterprise developed.[3] The extended notion of a paradigm was sufficiently vague, however, that it also became the focus of severe criticism and has largely ceased to figure in philosophical accounts of science.

Adopting the term *field* rather than discipline, Lindley Darden and Nancy Maull advanced a multifaceted conception in which no single element dominated (though it did not extend so far as to include externalist elements). Incorporating Shapere's notion of a domain, they defined a *field* as consisting of the following elements:

> a central problem, a domain consisting of items taken to be facts related to that problem, general explanatory facts and goals providing expectations as to how the problem is to be solved, techniques and methods, and sometimes, but not always, concepts, laws and theories which are related to the problem and which attempt to realize the explanatory goals. (Darden and Maull, 1977, p. 144)[4]

Especially relevant here are the explanatory goals, types of accounts offered (e.g., laws or theories), and conceptualization of the central problem, a cluster that I will call, for convenience, the field's *mission*. As I noted in Section 1, in many areas of biology explanation takes the form of an account of the mechanism responsible for a phenomenon. The central problem is then the discovery and refinement of this mechanism.

A second important component of fields, to which Darden and Maull drew attention, is its array of techniques and methods for solving problems. These

[3] Kuhn inspired several other attempts to characterize larger-scale units that served to unite the practitioners of a discipline. Two examples were Lakatos' (1970) notion of a research program and Laudan's (1977) notion of a research tradition.

[4] Shapere (1984) largely endorsed Darden and Maull's conception of a field but cautioned that one must be sensitive to the fluidity of fields and to the fact that often different practitioners within a field will not share exactly the same methods.

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are not just cognitive or reasoning strategies but include instruments, and techniques for using instruments, that enable the scientist to observe and manipulate objects in the domain. Ian Hacking (1983) pioneered discussion within philosophy of the importance of techniques for intervening in nature. Historians such as Kathryn Olesko have also emphasized the importance of techniques of investigation in delimiting a discipline. She nicely noted that a discipline *disciplines* its practitioners by requiring them to master a particular body of knowledge and techniques of investigation (Olesko, 1991, p. 14). Steven Shapin (1982), focusing on the differences between biometricians and Mendelians, illustrated the importance of differences in techniques and methods in demarcating these two groups of investigators.

In contrast, sociologists and social historians of science tend to focus on the social networks and institutional structures within which scientists work. One role such social units play can be related to the cognitive elements emphasized by philosophers and historians of ideas – they insure compliance with a discipline's mission and accepted methods. Thus, Michael Polanyi introduced "the principle of mutual control," which

> consists . . . of the simple fact that scientists keep watch over each other. Each scientist is both subject to criticism by all others and encouraged by their appreciation of him. This is how *scientific opinion* is formed, which enforces scientific standards and regulates the distribution of professional opportunities. (1966, p. 72)

This aspect of the social structure of disciplines was much emphasized by Robert Merton (1973) and the tradition in sociology of science which he inspired.

Subsequently, though, sociologists of science pushed beyond the Mertonian tradition to address how the institutional structure of disciplines influences the content of scientific research by, for example, focusing a particular scientist's endeavors. Rosenberg commented,

> It is the discipline that ultimately shapes the scholar's vocational identity. The confraternity of his acknowledged peers defines the scholar's aspirations, sets appropriate problems, and provides the intellectual tools with which to address them; finally, it is the discipline that rewards intellectual achievement. (1979, p. 444)

Contemporary sociologists emphasize that the factors that shape a scientist's identity are not limited to ideas internal to the science itself but can include those of the broader society. Thus, Robert Kohler characterized such institutions as "mediat[ing] between science and the political, cultural, and economic institutions on which science depends for material and support" (1982, p. 2). Accordingly, Kohler characterized disciplines such as biochemistry, on which he focused, as "political institutions that demarcate areas of academic territory" (p. 1).

Sometimes the emphasis on the roles played by the broader social, cultural, and economic institutions is presented as repudiating the significance of cognitive factors in shaping science (Barnes, 1977; Bloor, 1991; Collins, 1981; Latour & Woolgar, 1979). Such a stance has provoked equally ardent responses from philosophers who have construed any acknowledgment of social factors as undermining the epistemic warrant of science (Laudan, 1981; Kitcher, 2001; and several of the papers in Koertge, 1998). Other philosophers (Longino, 1990; Longino, 2002; Solomon, 2001) have developed a more moderate response, articulating how social factors figure in the intellectual development of science without sacrificing its epistemic warrant. While my sympathies lie with the last position, I will not advance arguments for it here; instead I will briefly discuss how scientists create institutions and how their decisions help shape research in a discipline.

The candidate political institutions of a discipline are academic departments, professional societies, and journals. Of these, departments are the most problematic for tracking scientific disciplines. There are a plethora of ways in which universities divide faculty into departments, often having to do with very local politics and ease of administration. Especially in the biological sciences, the differentiation into departments depends upon the size of the institution and whether the biological sciences are situated among the arts and sciences or in a medical school (or both). Small undergraduate colleges will typically group all the biological disciplines within one department, although they may have separate tracks for majors that correspond to divisions within biology. Research universities tend to have separate departments for different biological disciplines, although they may be grouped in pairs (e.g., cell and molecular biology, ecology and evolution). Although departments may not correspond exactly to disciplinary units as differentiated by such criteria as professional societies and journals, they ensure the historical continuity of disciplines by training subsequent generations of researchers and thereby securing the cognitive and social allegiances of members of a discipline. Richard Whitley commented, "Educational institutions form the basic commitments of scientists in nearly all fields, and constitute the fundamental unit of social and cognitive identity in the sciences, which is one reason why the term 'discipline' is usually understood to refer to units of organization in universities" (1980, p. 310).

Outside of the context of the local university, professional societies and journals are the major institutions that provide disciplinary identity. Given the importance of publication both in establishing a scientist's career and in disseminating results of research, the availability of journals influences the direction of a field. They determine not only what topics of research can most readily be published, but also what methods investigators can employ in investigating those topics. An important step in developing a new area of research and a research community that will carry out the research is the creation of new journals that will publish the results. In many cases, professional societies manage journals. Societies typically also hold regular meetings that provide a context in which scientists meet formally and informally to share results and formulate directions for future research. Although talks at professional society meetings often receive less credit in terms of professional advancement, they are favored vehicles for rapid communication and provide important opportunities for personal interaction.

Beyond formal institutions, sociologists have also focused on informal networks of scientists. Derek de Solla Price (1961; see also Crane, 1972; Chubin, 1982) coined the concept *invisible college* for groups of researchers who are in regular communication and share a common conceptual framework, problem focus, and set of techniques for dealing with a problem, although they may disagree on empirical claims or proposed theories. Sociologists identify such networks using such techniques as tracking citations and identifying clusters (Garfield, 1979). A variety of quantitative techniques have been developed for identifying and graphing social networks (Wasserman & Faust, 1994). A recent approach focuses on collaboration networks characterized in terms of coauthorship of papers (if two scientists have coauthored a paper, they are directly linked; if two scientists have not coauthored a paper but have each coauthored a paper with another scientist they are linked through that scientist, etc.). These networks have been shown to constitute structures known as *small worlds* in which randomly chosen pairs of scientists are typically separated by only a short path of intermediate collaborators (Newman, 2001). Such networks can also be studied more qualitatively and in detail to reveal the interactions that shape the direction of science. Jean-Paul Gaudillière (1996), for example, studied collaborative networks of scientists in France in the 1960s as specimens that could be revealing of the relationship between biochemistry and the emerging molecular biology.

As it turns out, despite the frequent conflict between theorists pursuing cognitive and social accounts of science, the various cognitive and social criteria for delineating units in science tend to converge on the same units. That is, institutional structures, methods of inquiry, domains of inquiry, and

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missions align closely enough that they can be treated as different aspects of the same unit. The contributors to a particular journal or members of a given professional society will tend to focus on a common domain of inquiry, share a common mission, and employ a similar range of techniques. Network analyses will likewise tend to track scientists who share many of these common characteristics. In the analysis of cell biology in this book, I will be focusing on three of the features of disciplines discussed above – the mission, research methods, and institutions. Together, these resulted in a discipline devoted to the domain of cellular mechanisms.

In the discussion so far I have not considered the generality or specificity of a discipline. Each of the criteria, however, can be applied so as to pick out units that vary considerably in specificity or scope. Focusing just on professional organizations, some (such as the American Association for the Advancement of Science or The Royal Society) attempt to serve the whole of science, others (such as the Biochemical Society and the American Society for Cell Biology) have a more limited scope, and still others focus on specific phenomena (the Protein Society or the RNA Society) or techniques (The Tissue Culture Association or the Electron Microscope Society of America). Though terminology for units at different levels of generality involves very fuzzy, overlapping boundaries, the range from most to least general might be taken to include (1) molar disciplines (e.g., biology, chemistry); (2) operational units called either disciplines or fields[5] (e.g., ecology, cell biology, biochemistry); (3) research areas[6] that focus on particular phenomena within the scope of a discipline (these can be rather slippery; e.g., the research areas of intermediary metabolism and cellular respiration have overlapped in different ways at different times); (4) smaller units that can be delimited by time, space, subdomain, or affinity (e.g., the Institute for Enzyme Research at the University of Wisconsin; (5) finally, the individual investigator or research team.

Several levels in this hierarchy are relevant for understanding the creation of cell biology. At various points I will be focusing on individual scientists and laboratories and will discuss several research areas. But cell biology

[5] In definitions and in actual use, these terms overlap substantially but not completely. For example, disciplines may tend toward greater size or tighter ties to institutional structures than fields. Any such differences need not be adjudicated here.

[6] They are called *research areas* to help distinguish them from the larger fields to which they belong, but are similar in meaning to *research fields* or *scientific specialties*. Historian of science Larry Holmes offered this discerning characterization: “A research field is more than a network of communication and ties of professional interest. It is also an ongoing investigative stream composed of the intersecting investigative pathways of each of the individual scientists (or integrated local research groups) who participate actively at its creative forefront” (1992, p. 7).

itself is a discipline or field that incorporated a number of research areas. The institutions developed to serve it, especially the American Society for Cell Biology and the *Journal of Cell Biology*, took as their focus investigations into the various organelles of the cell and their functioning. Even when they worked in different research areas, the investigators who affiliated with these organizations shared a common mission of understanding the structure and function of the mechanisms comprising cells. They also shared a number of research instruments and techniques, especially electron microscopy and cell fractionation.

Accounts of disciplines sometimes treat them as eternal, non-temporal entities. My reference to the creation of cell biology beginning in the 1940s highlights the fact that they are historical entities. Starting in the nineteenth century new disciplines have repeatedly arisen. New disciplines or research areas can emerge for any one of a number of reasons. Sometimes a particular investigative strategy and a mission and domain adapted to it arise within a discipline and the divergence is not comfortably accommodated (e.g., molecular biology arose in part from biochemistry but separated, producing an uneasy relationship for many years).[7] Sometimes a genuinely new domain comes into existence along with people, methods, and a mission (e.g., the rise of computer science in the mid-twentieth century). A very common pattern, though, is for new disciplines to emerge in an unoccupied domain lying between existing disciplines for which no existing discipline possesses the needed research tools.

Research in contemporary science is often interdisciplinary in character, and interdisciplinarity is often touted as a virtue. But there has been little discussion of the desired outcome of interdisciplinary research. The best account remains Darden and Maull's (1977) account of what they called *interfield theories*. They described an interfield theory as "a different type of theory . . . which sets out and explains the relations between fields" (p. 48). They suggested and discussed several types of interfield relation: (a) structure-function, e.g., physical chemistry targets the structure of molecules while biochemistry describes their function; (b) physical location of a postulated entity or process, e.g., the chromosomes identified in cells by cytologists provide the physical location of the genes postulated by geneticists (a case that also exemplifies structure–function and part–whole relations); (c) physical nature

[7] There are numerous books and papers on this case, but see especially the Fall 1996 special issue of *Journal of the History of Biology*, 29 (3), on "The tools of the discipline: Biochemists and molecular biologists." Rheinberger, Chadarevian, Gaudillière, and Burian emphasized methods and Creager, Gaudillieère, and Kay attended particularly to individuals and institutions.

of a postulated entity or process, e.g., biochemistry specifies the physical realization of entities postulated by the operon theory in genetics; (d) cause–effect; e.g., biochemical interactions are a cause of heritable patterns of gene expression. More recently Darden (Darden & Craver, 2002; Darden, 2005) has emphasized mechanisms as a frequent focus of interfield theories, and indeed, all four of these relationships figure in accounts of mechanisms.

My interest here is not in interdisciplinary research generally, but rather in interdisciplinary research that gives rise to a new discipline. New disciplines do not always result even if the interdisciplinary engagement is maintained over a long period of time. In Bechtel (1986a) I contrasted cases such as cognitive science, in which scientists maintained their primary allegiances to the contributing disciplines (e.g., psychology, artificial intelligence, linguistics), with cases such as biochemistry, in which a new discipline developed that secured the primary commitment of future practitioners. I characterized the former as *interdisciplinary research clusters*. Although they develop similar institutional structures as disciplines (professional societies and journals) and are interested in a common domain of phenomena, clusters do not employ distinctive research techniques. Rather, collaborators draw upon the techniques and employ the standards of successful explanation from their home disciplines. Collaboration is motivated by the advantages of coordinating the results of multiple disciplines in understanding a phenomenon of common interest.

Interdisciplinary research gives rise to new disciplines when research addresses phenomena that are not the focus of any of the contributing disciplines and involves new research tools and techniques that facilitate the new inquiry. These also enable researchers to pursue explanatory goals that are not those of any of the existing disciplines. When new institutional arrangements are developed, they tend to become the primary institutional home of the practitioners and they will characterize themselves using the name of the new discipline. This, I will argue, is what happened in the case of cell biology.

3. THE NEW DISCIPLINE OF CELL BIOLOGY

By the late 1960s cell biology had acquired the characteristics I identified for disciplines in the preceding section. Cell biologists pursued a distinctive domain (cell organelles and their functions), employed a new set of tools (especially electron microscopy and cell fractionation), pursued a distinctive mission (determining the mechanisms that enabled organelles to perform their functions), and created new professional institutions (especially journals and professional societies). This process began in the 1940s, and thus I have chosen the period 1940 to 1970 as the scope of my inquiry. In many respects, though, the endeavors of cell biologists were continuous with those of earlier scientists: Cells and their internal structure had been the focus of extensive investigation in nineteenth-century cytology. Yet, the name *cell biology* was deliberately chosen to demarcate the new discipline from cytology. Another discipline, biochemistry, had established itself at the beginning of the twentieth century to study the chemical activities within cells, with a particular focus on enzymes, and achieved remarkable success in its first four decades. Chapter 3 reviews these accomplishments, showing that each of these disciplines already was addressing aspects of what was to become the domain of cell biology: cell structures in cytology and chemical operations associated with cell structures in biochemistry. However, proceeding on their separate paths, they failed to integrate findings on cell structure and function into a unified account. Moreover, as noted above, a discipline is more than a domain. What most clearly differentiated early cell biology from both cytology and biochemistry was the nature of the investigations cell biologists pursued and the tools they employed.

The investigators who created cell biology were strongly committed to inquiry that related knowledge of the parts of the cell (organelles) and the chemical operations that took place in those parts. The methodologies that had been so successful in the early decades of biochemistry involved extracting the responsible enzymes and substrates from cells and studying reactions that did not depend on the specifics of cell structure. So for many biochemists, cells were unimportant. A number of cytologists, on the other hand, were eager to relate cell parts to chemical operations, but for the most part they lacked the tools to make the connections. Thus, despite the focus on cell structure and function by cytology and biochemistry, Chapter 3 shows that in 1940 there remained a terra incognita between these two fields.

Integration of cytological and biochemical approaches were critical for investigators to understand many of the mechanisms responsible for cell activities. However, there is one conspicuous instance of a cell mechanism for which cytologists figured out the basic mechanism schema without reliance on biochemistry – cell division. With the introduction of new dyes in the late nineteenth century, researchers such as Edouard van Beneden, Hermann Fol, and Walther Flemming were able to identify chromosomes in the cell nucleus and determine the sequence of operations in which they figured in cell division. Further, August Weisman and others recognized linkages between chromosomes and hereditary material, and Carl Correns determined how the events of cell division ensured the transmission of hereditary factors to daughter

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cells. To discover that DNA was the hereditary material and determine the mechanism by which it replicated, new tools had to be developed. This was done by molecular biologists in the 1940s and 1950s, but from the point of view of cell mechanisms, those discoveries filled in the schema developed much earlier (Darden, 2005). I will briefly analyze this case in Chapter 3, but otherwise my focus will be on mechanisms situated in the cytoplasm of the cell, that is, all of the cellular materials enclosed within the cell membrane excepting the nucleus.

The cytoplasm is the locus of a host of cellular mechanisms that are responsible for taking in material from the cell's environment, breaking down this material as well as worn out pieces of its own structure, and synthesizing new components of its own structure or materials for export out of the cell. All of these mechanisms require energy; accordingly, several additional mechanisms are devoted to procuring and making energy available to them. To understand any of these mechanisms, it was not enough to have ideas about the phenomena they produced; scientists needed means of investigation. With the development of stains in the late nineteenth century, cytologists began to secure evidence of the occurrence of structures, called *organelles*, in what until then had appeared as formless cytoplasm. However, the evidence was highly contested and would be until techniques became available that went beyond those of light microscopy. Biochemists, on the other hand, routinely destroyed cell structure because it provided the best means of securing preparations in which they could study chemical reactions. To link reactions to the particular organelle in which they occurred (and in some cases to study them at all) required more refined preparations. Two instruments developed by physicists and chemists in the 1920s and 1930s offered promise for entering these unexplored territories – the electron microscope and the ultracentrifuge. Biologists, however, confronted significant challenges in developing the techniques needed to deploy these instruments to study mechanisms operative in cells. These challenges and the techniques that were created to surmount them will be examined in Chapter 4.

New research techniques pose both an engineering and an epistemic challenge. As in prototypical engineering tasks, in order to use the ultracentrifuge or the electron microscope, researchers had to figure out ways to accomplish new tasks – for example, to release the contents of cells from the cell membrane without disrupting internal structures and to stain cell components so that they would differentially diffract electrons. Engineering tasks like these give rise to the epistemic challenge of showing that the results reflect the phenomenon of interest and are not artifactual. Because the evaluation of engineering solutions is frequently grounded in empirical exploration, rather

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than in detailed knowledge of how the techniques work, scientists use indirect measures to answer the epistemic challenge. Chapter 4 will focus on three such indirect measures used by cell biologists – the determinateness and repeatability of the resulting evidence, consilience of evidence from multiple techniques, and the coherence of the evidence with plausible accounts of the mechanism under study.

In Chapters 5 and 6 I turn to how these new techniques were deployed to better understand cell mechanisms.[8] Chapter 5 concentrates on one laboratory located at the Rockefeller Institute that conducted many of the pioneering inquiries. The initial focus of this laboratory was cancer. Albert Claude centrifuged tumor cells in an attempt to find within them particles involved in the transmission of cancer. When the particles he discovered turned out not to be unique to cancer cells, he shifted his attention to studying those isolated from normal cells. Collaborating with chemists, he identified the chemical reactions associated with centrifuged fractions containing those particles. In collaboration with Keith Porter, he also began employing electron microscopy to compare the particles in the fractions with components of intact cells to determine their origins. A major accomplishment of this research was to demonstrate that a fraction that was highly specific for a certain cell organelle – the mitochondrion – contained the critical enzymes involved in cellular respiration. Mitochondria were dubbed the power plants of the cell, and they became a focus of the analytic powers of cell biologists.

Chapter 6 describes how in the 1950s and 1960s a growing cadre of researchers adopted the techniques of electron microscopy and cell fractionation and pursued the project of explicating the mechanisms operative in the cell cytoplasm. Figure 1.1 is a drawing portraying the organelles known to populate the cell that is representative of those offered by cell biologists based on the electron micrographs produced in the 1950s. Cell biologists and biochemists both contributed to increasingly fine-grained accounts of the structures within mitochondria and their roles in biochemical operations. A crowning achievement was the discovery that certain key enzymes were embedded in the inner membrane of the mitochondrion so as to spatially and temporally organize the reactions involved in electron transport and oxidative phosphorylation. The work with mitochondria provided an exemplar (in Kuhn's sense) of how to link functions with organelles that became a model

[8] Treating the development of new instruments and research techniques separately from their utilization in developing new knowledge is artificial because the investigators were putting their techniques to use to secure information about cell mechanisms as they were developing them. I have discussed them separately so as to do justice to the different epistemic issues involved in developing the techniques and using them to understand mechanisms.

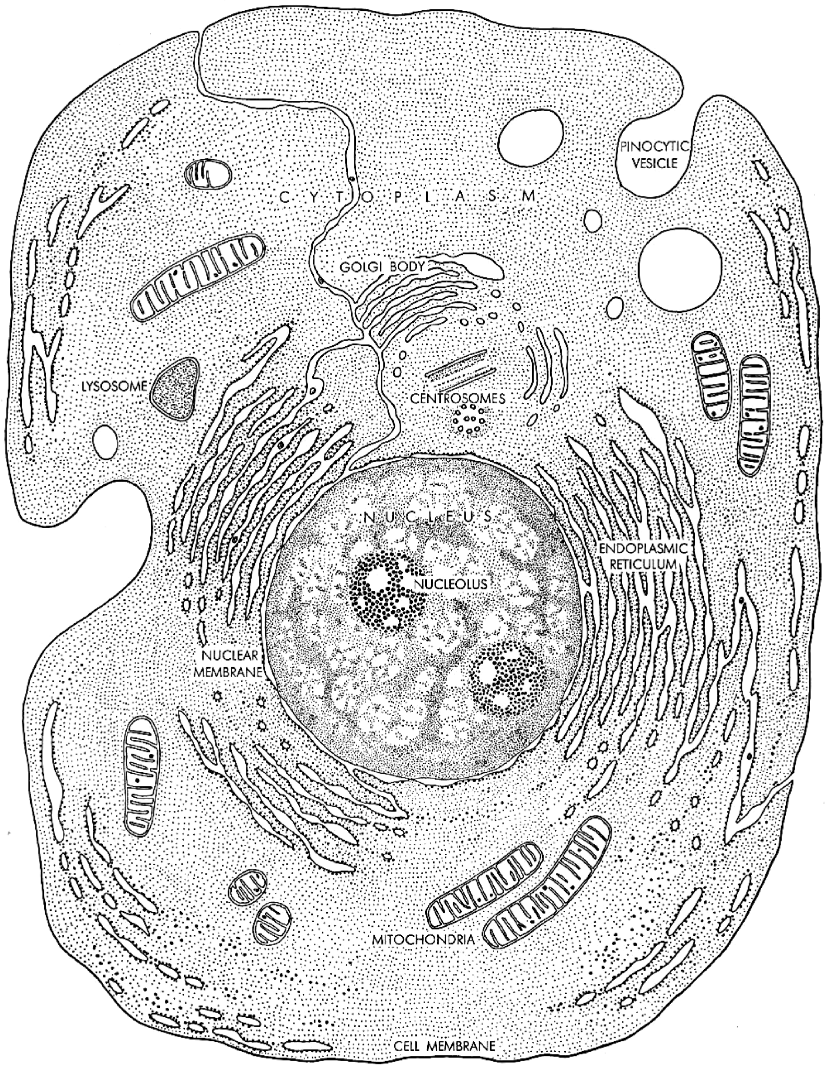

Figure 1.1. Diagram of a typical cell based on electron micrographs available in 1960. The four organelles that are the focus of the analysis in subsequent chapters – the mitochondrion, endoplasmic reticulum, lysosomes, and Golgi body (Golgi apparatus) – are clearly delineated. Reprinted from Jean Brachet (1961), The living cell, *Scientific American*, *205* (3), p. 7, with permission of Donald Garber, Executor of the Estate of Bunji Tagawa.

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for investigations of other cell organelles and their functions, including the role of the ribosomes and endoplasmic reticulum in protein synthesis, the Golgi apparatus in cell secretion, and the lysosome in recycling cell waste.

As I discussed in the previous section, an important aspect of scientific disciplines is the creation of institutional structures. In the 1950s, research in the new discipline of cell biology was becoming highly specialized. It also fell sufficiently outside the scope of existing disciplines that numerous scientists felt the need to create new journals. The *Journal of Biophysical and Biological Cytology* was established in 1956 and rapidly established itself as the premier journal for the new community. In 1962 it changed its name to the *Journal of Cell Biology*, thereby recognizing the name increasingly favored for this discipline. The growing community also felt the need for regular scientific meetings; in 1960 they founded the American Society for Cell Biology. Creating a journal and a society were not small undertakings but required scientists to take substantial amounts of time away from research. The character of the journal and the society, moreover, were not foreordained, but resulted from explicit deliberation by these pioneers in cell biology. Chapter 7 will examine the processes involved in creating and nurturing the new journal and new society.